The mechanisms of ventricular arrhythmia in Chagas disease

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Chagas disease remains an important health problem in South, Central and some parts of North America. It is caused by infection with the protozoa *Trypansoma cruzi* and the disease has an initial acute phase followed by chronic infection in the absence of appropriate treatment [1;2]. In the chronic phase of the disease 20-30% of patients can develop a cardiomyopathy [1;2]. It is generally thought that the *Trypansoma cruzi* parasite is able to evade immune clearance. This leads to a chronic inflammatory response within the myocardium characterised by infiltration of various T-cell subtypes and release of inflammatory mediators including IL-18, TNF-α and TGF-β [2]. The latter is thought to be a key driver of the inflammatory and fibrotic response [2]. The development of the cardiac disease is highly variable but at its' worse it can result in a disease resembling dilated cardiomyopathy with ventricular aneurysms and severe heart failure [1;2]. Cardiac arrhythmias are a prominent feature of the disease and include bradycardia, heart block, atrial fibrillation, bundle branch block, ventricular ectopics and malignant ventricular arrhythmias leading to sudden cardiac death [1;2].

In this issue of the journal, Medei and colleagues look at a specific feature in the pathogenesis of the arrhythmic diathesis. The authors have previously described an interesting feature of the immune response in Chagas cardiomyopathy patients namely the production of autoantibodies particularly to the β adrenergic receptor [3]. The presence of autoantibodies correlated with the risk of arrhythmia occurrence in patients. However in normal rabbit hearts addition of the patient sera did not lead to the induction of arrhythmia and only modest electrophysiological abnormalities [3]. The current paper now extends this work. They use a well-established pharmacological model of hereditary long QT syndrome (LQTS2) in which isolated rabbit hearts are treated with E-4031 which is a specific inhibitor of HERG potassium channels; a key repolarising current [4;5]. In this setting the application of the patient antisera led to shortening of the QT interval but increased Tpeak-Tend, a

marker of the spatial dispersion of repolarisation. Furthermore, the antisera induced ventricular rhythm disturbances including ventricular ectopics, ventricular tachycardia and torsade-de-pointes and AV nodal block. Finally, ventricular action potentials were measured using sharp microelectrodes in muscle strips and the combination of E-4031 and the patient antisera led to early afterdepolarisations. Control antisera did not lead to these effects and the effects were reversed by a β-blocker.

The paper makes a plausible case for a contribution of this mechanism in addition to the fibrosis and structural heart disease. Indeed the early afterdepolarisations could precipitate re-entry in hearts with significant structural damage. It is known that the QTc interval is prolonged in chronic cardiac Chagas disease and thus in the diseased heart this may interact with the autoantibodies stimulating the β-adrenergic receptor to promote arrhythmia [2]. Furthermore, increased adrenergic drive is known to be proarrhythmic in a variety of settings including in the long QT syndrome [5]. It also leads to some therapeutic considerations. The management of heart failure associated with Chagas cardiomyopathy is very much treated along standard lines [2]. β-blockers are used and the results of this study support that approach. However their use can be complicated by the brady-arrhythmias associated with the disease. Patients with the hereditary long QT syndromes are advised to avoid certain drugs (http://www.sads.org.uk/drugs-to-avoid/) and where good alternatives exist it may be prudent to take this precaution.

The paper uses rabbit *ex-vivo* preparations with the acute addition of patient derived sera. In humans with the disease other considerations may be at play in the genesis of the arrhythmia. Patients with Chagas disease have a blunting of autonomic control of cardiac dysfunction is present [6]. Sympathetic tone probably declines later compared to other causes of heart failure [7]. The dysautonomia likely occurs because of the inflammatory process damaging nerve termini and plexi in the heart. Furthermore, autoantibodies have been

described to muscarinic as well as adrenergic receptors in this disease [3]. In-vivo, the chronic production of autoantibodies may rather lead to receptor desensitisation and degradation and contribute to the dysautonomia. It is impossible to test this except in some kind of animal model of the actual infective disease. However, Medei and colleagues make an interesting contribution to the understanding of arrhythmia in Chagas disease emphasising how different substrates may interact.

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